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Fecal microbiota transplantation: Uses, questions, and ethics

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Abstract

Fecal microbiota transplantation (FMT) has rapidly grown in notoriety and popularity worldwide as a treatment for both recurrent and refractory *C. difficile* infection (CDI), as well as for a myriad of other indications, with varying levels of evidence to justify its use. At present, FMT use in the U.S. has not received marketing approval from the U.S. Food and Drug Administration (FDA), but is permitted under “enforcement discretion” for CDI not responding to standard therapy. Meanwhile, the rising interest in the gut microbiome throughout mainstream media has paved the way for “do-it-yourself” (DIY) adaptations of the procedure. This access and unregulated use, often outside any clinical supervision, has quickly outpaced the medical community’s research and regulatory efforts. While some studies have been able to demonstrate the success of FMT in treating conditions other than CDI—studies on ulcerative colitis have been particularly promising—little is still known about the treatment’s mechanism of action or long-term side effects. Likewise, screening of donor stool is in its early stages in terms of protocol standardization. In this paper, we explore the regulatory and ethical concerns that arise from the need to balance access to a nascent but promising innovative treatment with the need for research into its efficacy, risk profile, and long-term impact.

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Keywords

Gastrointestinal microbiome; *C. difficile*; Investigational drugs; Expanded access; Bioethics; Regulation

1. Introduction

The human microbiome, or community of microorganisms that reside on and within us, has become a rapidly growing area of study with exciting therapeutic prospects. With the human body hosting a nearly equal ratio of bacterial to human cells [1], understanding our cohabitants and the host-microbiome relationship could elucidate how microbes might cause, treat, modulate, or even prevent disease. One of the most well-known forms of microbiome-based therapy is fecal microbiota transplantation (FMT), in which a fecal suspension from a healthy donor is deposited into the gastrointestinal (GI) tract of a patient via endoscope, nasal tube, or capsule. The efficacy of FMT in combating *C. difficile* infection (CDI) has resulted in significant improvements in patients who have had either an inadequate response to traditional antibiotic therapies (i.e. refractory disease) or recurring infection after presumed successful treatment (i.e., recurrent disease) [2–5]. Both of these conditions are considered CDIs not responding to standard therapy, although most FMT research is focused on recurrent rather than refractory infections [2–4]. As interest in FMT and evidence of its ability to alter intestinal microbiome composition and/or function grows, enthusiasm about its applications beyond CDI is inevitable. However, FMT has not received marketing approval from the US Food and Drug Administration (FDA) for any indication; rather, the regulatory body has chosen to exercise “enforcement discretion” for FMTs performed for refractory and/or recurrent CDI. FMTs for other indications besides CDIs require that investigators obtain investigational new drug (IND) applications. A unique aspect of FMT, however, is that it can be performed outside of a professional medical facility as a “do-it-yourself” (DIY) procedure [6]. Clinician reluctance to perform FMT in situations, whether based on lack of safety and efficacy data or due to the burden of undergoing an IND application, may have the unintended consequence of increasing the number of patients performing at-home variants of FMT without the guidance of a medical professional [6–8]. It is amidst this backdrop that we review FMT’s current applications within the United States (U.S.) and its therapeutic potential; its unanswered safety, efficacy, and regulatory concerns; and the ethical challenges raised by the procedure.

2. Current applications and therapeutic potential

Dating as far back as the times of ancient China, preparations of fecal solution were orally administered to treat gastrointestinal diseases [9, 10]. Stanley Falkow, the famed American microbiologist and father of molecular microbial pathogenesis, recalled working with an internist in 1957 to give patients capsules containing a formulation of their own pre-surgical stool in an attempt to combat antibiotic-associated diarrhea [11]. The following year, surgeon Ben Eiseman reported the first official use of fecal enemas in the U.S. as a successful treatment for pseudomembranous enterocolitis [12], now more commonly known as *Clostridioides difficile* (*C. difficile*) colitis.

To date, most FMT research has pertained to *C. difficile*, an anaerobic, spore-forming, Gram-positive bacillus, which is transmitted via the fecal-oral route. Individuals with altered GI microbiomes, often in association with antibiotic use, are particularly vulnerable to this infection [13]. Once established in the gut, *C. difficile* can cause enteric disease ranging from mild diarrhea to a life-threatening infection. CDI is furthermore a common cause of nosocomial infection [14–16]. Risk of disease recurrence is high, and patients with a history of 2 or more CDIs have a 65% risk of further episodes despite antibiotic therapy [17].

Despite the lack of any large, randomized control studies (akin to typical Phase 3 clinical trials needed for FDA approval of a treatment), multiple smaller-scale studies have shown FMT to be an effective alternative to standard antibiotics for patients with recurrent CDI [2,18–21]. In a randomized control trial (RCT) for subjects with recurrent CDI for whom standard antibiotic therapy had failed, vancomycin treatment followed by up to 2 FMT procedures led to disease resolution for at least 10 weeks in 98% of subjects compared to 31% of those treated with vancomycin alone [2]. Another double-blind RCT compared donor stool to autologous stool (i.e. inert comparator) for recurrent CDI, finding 90% resolution after donor stool—though, interestingly, 62% of the autologous treatment group were also cured [4]. Given mounting evidence pointing to FMT as a durable treatment for recurrent CDI, with typically only mild short-term adverse effects such as abdominal cramping [3,19], clinicians may be more willing to suggest FMT to treat CDI, even for pediatric patients [22].

Accordingly, academic studies of microbially-based therapies have grown rapidly. Published clinical trials using the term “fecal microbiota transplantation” first appeared in the PubMed database in 2014. Since then, 87 additional FMT-related clinical trials have been published: 78 within the last 5 years and 21 in 2019 alone. Non-CDI indications for which FMT has been considered span as widely as obesity, allergies, neurological and behavioral disorders, and multiple bowel and immune-mediated disorders [8,23–33].

3. Public perception

The rise of FMT comes at a time when public access to medical information is relatively unfiltered, of varying levels of scientific accuracy, and widely disseminated via the internet and social media. According to a 2017 survey by the Pew Research Center [34], a majority of respondents reported that they “do their own research in addition to seeking advice from a doctor or other health care provider” when making decisions about treatment for a serious health problem. Furthermore, about half of the respondents reported having tried some form of alternative medicine—for example, herbal remedies, acupuncture or chiropractic treatment, or energy therapies.

While reports of FMT success are understandably compelling, patient (and sometimes provider) perceptions are saturated with the idea of FMT as natural, safe, and somehow intangibly separate from conventional medicine [[6–9]]. The gut microbiome’s role in health and disease has captured mainstream interest, enjoying no small media popularity, with a subsequent boom of an entire industry focused on probiotics, prebiotics, medicinal foods, and other formulas promising to restore and/or improve one’s microbiome [35].

In 2017, Park et al. [36] found that while only 12% of surveyed subjects initially knew of FMT as a therapeutic option for CDI, once informed, 77% would undergo the procedure if medically indicated. Studies since then have seen increasing proportions of both previous knowledge of and personal interest in the therapy [31–33]. Yet this favorable disposition to FMT, particularly when based on such sources as social media or personal anecdotes, may unintentionally serve to distract the public from long-term implications of the procedure, such as untoward or unintended changes in the gut microbiome [8,35,37].

Thus, increased research into FMT, its potential applications, long-term impact, and mechanism of action is both warranted and timely. Furthermore, the need for thoroughly vetted regulations and guidelines will have to be balanced with the reality that donor stool will always be obtainable to individuals willing to engage in DIY FMT, limiting the effectiveness of attempted “gatekeeping” on the part of either clinicians or regulators.

4. Unanswered questions

For all its utility in the treatment of recurrent CDI, there remain significant unanswered questions regarding FMT, including whether it works for other indications and its long-term physiological effects. With emerging evidence that gut microbes are able to dictate the induction of Th17 cells, which play a role in mucosal defense and the pathogenesis of autoimmune disease [38], the mechanisms by which gut microorganisms can impact health and disease are still largely unknown. It is furthermore debated whether the induction of an unedited donor sample is required for successful FMT [9] or whether a select consortium of bacteria, bacterial spores, and/or the degree of donor microbiome engraftment are the true determinants or modulators of FMT outcomes [39–42]. Similarly, advances in fecal preparation methods, including automated washing of fecal suspensions, have been shown to reduce the load of viruses and inflammatory cytokines which may be associated with FMT risks [43,44]. Microbial transfer technologies are growing in sophistication, with newer products tailoring the product delivered beyond donor stool. For example, the probiotic strain *Escherichia coli* Nissile has recently been engineered to act as targeted immunotherapy for treating certain cancers and for the congenital disorder phenylketonuria [45,46].

We also do not currently understand how to select for an ideal FMT recipient or how other underlying conditions might impact response [41, 42,47]. Similarly, little is known about what qualifies as an effective or safe donor, beyond the general idea of good health and screening for a select subset of transmissible pathogens. Finally, it must be acknowledged that questions regarding donor and recipient selection, mechanism of action, and best practices may be indication-specific.

4.1. Long-term risks

While information on long-term effects of FMT in humans is sparse, several animal models have shown that FMT can transfer disease phenotypes such as obesity and metabolic disorders [48–54]. Other animal studies demonstrate the impact of other gut microbiome alterations—such as antibiotic exposure or cecal content transfer—on disease phenotype, such as increasing the risk for colitis [50,55,56]. Gut bacteria have also been implicated in

the risk of heart disease and colon cancer [53,57,58]. One well-publicized case study documented a patient who developed new-onset obesity after receiving stool from a healthy but overweight donor [59]. This transferability of obesity with, to-date, no biochemical marker for which to screen donor stool, raises concerns about what phenotypes may escape detection and subsequently be transmitted via FMT.

While the risk of acquiring conditions that do not manifest for many years may be largely irrelevant for an elderly population, FMT is also currently used in young adults and children. Such use is of concern because of the scarcity of data on potential long-term physiological, metabolic, and immunologic effects of FMT. Studies have already demonstrated that the gut microbiome in early life is both strongly susceptible to perturbations [60] and also a possible driving force in immune development [61]. Thus, a child undergoing FMT may be risking microbiome alterations that could influence the risk of disease in adulthood. In cases where no other therapy is effective, this may be a tradeoff that clinicians and patients, or their guardians, are willing to accept. However, there are increasing requests for FMT as a first-line therapy or for non-CDI indications [6,8]. For these indications, use of FMT is unjustified outside of a clinical trial, given the limited supporting data and the availability of other, better-researched treatment alternatives.

Additional work is needed to examine the potential of FMT to contribute to multifactorial diseases such as diabetes or cardiovascular disease, in which disease pathogenesis may take place over decades rather than the comparatively limited timescale of currently available FMT studies. In addition, given the high prevalence of these diseases, efforts to isolate a possible connection with FMT in a clinical context will require careful study design and data collection and will likely require a multicenter effort to enroll sufficient subjects; such a task will take significant time, funding, and collaboration to complete.

4.2. What constitutes thorough screening of donor stool

While there is no universally validated and adopted screening protocol for stool donors, most centers that conduct FMT require donors to undergo blood testing for HIV, hepatitis A, B and C, and stool testing for salmonella, parasites, and *C. difficile*, among other pathogenic organisms [62,63]. For one large public stool bank, only 8.5% of asymptomatic potential donor samples were ultimately accepted, often due to the incidental detection of possible gastrointestinal pathogens [64].

In addition, in 2019, there were two well-publicized cases of multi-drug resistant organism (MDRO) infections attributed to FMT, one of which led to the patient's death [65]. These cases led the FDA to revise its guidance [66]—continuing the policy of enforcement discretion which allows the use of FMT for CDI indications, but mandating additional screening for MDROs. While these cases highlight the long-suspected potential for severe adverse effects related to FMT, they also highlight the tenuous access patients have to acceptable FMT product, particularly as some of the required screenings—such as for fecal extended spectrum beta-lactamase (ESBL)-producing organisms—do not have well-established clinical laboratory protocols, even at large academic medical centers.

Current screening protocols may be insufficient, however, and do not account for the possibility of gut microbiome perturbation through a mechanism other than a known infectious agent. In this respect, FMT today resembles the nascent stage of blood transfusions in the 1940s and 1950s, before testing for such blood-borne diseases as human immunodeficiency virus (HIV), human T-cell leukemia virus (HTLV), and hepatitis B and C was possible [67]. The inadvertent transmission of a harmful agent via a biological treatment was poignantly demonstrated in the transmission of HIV via contaminated Factor VIII used by patients with hemophilia [68]. Thus, FMT donor stool screening and quality control should reflect the gravity of these potential risks.

Furthermore, while medical institutions do screen donor stool prior to transplantation, DIY FMT may not involve any screening at all, or at best rely on unreliable claims of laboratory testing. In an appeal for donations to pay for FMT to be done by a medical provider at a hospital with standardized donor testing, a patient reported that she had “tried FMT from home in the past, but that was a nightmare as the only donor that met the criteria (and that I was paying money to) lied to me about their test results ... [and] ... had parasites” [69]. Such anecdotes cannot quantify the scale of the problem of insufficiently screened donor stool being used in DIY FMT attempts, but they do paint a picture of this very real concern.

4.3 Demand for Applications Beyond C. difficile.

A further question raised by FMT is whether its success in treating CDI can translate into success for other indications. Studies to determine FMT efficacy for a range of indications are in progress, but at this point, there are insufficient clinical or preclinical data to justify FMT in non-CDI contexts outside of clinical trials. Nevertheless, there is anecdotal evidence that such innovative therapeutic attempts are being made, with and without physician oversight.

A search of the GoFundMe crowdfunding platform for US-based medical campaigns that referenced “FMT” found it proposed as a therapy not only for CDI but also for ulcerative colitis; autism spectrum disorders; fluoroquinolone toxicity; mast cell activation syndrome and dysautonomia; chronic pain; chronic pouchitis; and combinations of complex medical disorders. Of these various campaigns, two specified that the FMT would be undertaken outside of the United States (Canada, Argentina), while one mentioned a DIY FMT attempt. Only one campaign referenced FMT in the context of a clinical trial [70]; none mentioned a clinician procuring the FDA-required IND. These cases represent only a small subset of all FMTs performed or considered, but they highlight the many complex issues surrounding the field, including cost and safety. Outside of clinical trial settings, the FDA permits use of FMT that is strictly limited to select CDI indications; yet, as stool is readily available, it is impossible to control who is conducting FMT, for what indications, and with what safeguards.

4.4. Regulatory status

While FDA approvals of products are for certain indications (“on-label uses”), physicians have the prerogative to prescribe these products for “off-label use” however they feel fit, so long as they can defend themselves from potential legal charges that they deviated from the

standard of care without cause. Thus, the FDA regulates when a new medical product may come to market, not the medical practice of its use. Given the ubiquitously available nature of stool, the agency's role in preventing access to this unapproved medical product is significantly undermined. The regulatory status of FMT is made even more problematic by the fact that the FDA determined that fecal microbiota falls into two classes: both that of “drug” and “biological product” [71].

In 2013, the FDA declared that a physician or a company must obtain an IND application to perform FMT. Investigators and clinicians alike pushed back, stating that clinical experience and early data for FMT already demonstrated its effectiveness as treatment for recurrent or refractory CDI, and that the regulatory burden of maintaining an IND may prevent many clinicians from providing a potentially life-saving therapy [72]. In acknowledgement of this concern, the FDA announced that it would exercise enforcement discretion for FMTs performed for CDI not responding to standard therapy [73]. However, the agency maintained that use of FMT for research or to treat conditions other than CDI would require an IND.

Typically, an IND is secured in order to conduct a clinical trial; less commonly, INDs (including for the treatment of single patients) may be obtained via FDA's Expanded Access (“compassionate use”) pathway [74]. An eligible patient would have to have no approved therapeutic options, be ineligible to participate in a clinical trial, be seriously or life-threateningly ill and deemed more likely to benefit than to be harmed from the unapproved treatment, and have a treating physician willing to seek a single patient IND from the FDA and approval from an institutional review board (IRB). The patient, or a legally-appropriate surrogate decision maker, would be required to provide informed consent, and any serious or unexpected adverse events deemed related to the FMT would need to be reported promptly to the FDA. It is preferable to enroll a patient in a clinical trial whenever possible, in order to accrue scientifically useful data; however, a clinician may seek a single-patient IND for patients without other options.

In March of 2016, the FDA drafted revised guidance regarding clinical use of FMT for CDI. This guidance, though ultimately never implemented, would have allowed for continued enforcement discretion, provided that clinicians obtain informed consent, the donor stool is obtained from a donor known to either the patient or the treating health care provider, and the donor and the donor stool are screened under the direction of the health care provider [71]. Following the aforementioned two cases of MDRO infections attributed to FMT in 2019, according to the FDA, all potential FMT donor stool must be tested for MDROs. Additionally, the donor screening and stool testing processes—as well as the potential risks of MDRO transmission and invasive infection—must be explicitly addressed in the informed consent process for all patients potentially undergoing FMT [75].

Regulatory violations regarding the use of FMT for indications other than CDI must be stemmed, either by enforcement of the IND requirement or by broadening permissibility of FMT outside of clinical trials. The lack of concordance between regulation and policy is not only a legal matter but also an ethical one, and may contribute to FMT recipients’ overestimating the safety of the procedure. However, regulating FMT to the point that clinicians are unwilling or unable to provide the procedure will likely lead to greater

morbidity and mortality from CDI, as well as increased numbers of individuals pursuing DIY treatments [76].

5. Ethical concerns

As is often the case with new medical innovations, enthusiasm for FMT has outpaced available evidence of its efficacy and safety in treating a wide array of indications, thus raising ethical concerns [77–79]. The current popularity of FMT and the expansion—both in number and indication—of its use without FDA approval mirrors the initial and persistent popularity of many direct-to-consumer stem cell-based interventions. In both cases, treatment for some indications is evidence-based, while treatment for others reflects practitioners’ over-eagerness to treat a wide array of indications among credulous patients who are often desperate to believe these therapies offer cures to their ailments.

5.1. Informed consent

Informed, voluntary consent on the part of a patient is necessary for both research and clinical care. FMT exists in a no-man’s land between the two: Unless done in a clinical trial, it is performed as treatment that, although innovative, is considered non-standard of care. Even for CDI, FMT is not an FDA-approved therapy but rather merely permitted via the agency’s discretion. As there is not a definitive consensus regarding the specific impact of gut microbiome perturbations on short-and long-term systemic health, and with uncertainties about long-term risks from stool transplantation, properly informing patients about the risks and benefits of FMT is challenging.

In a rapidly evolving field where clinical experience is not always in step with discrete understanding of therapeutic mechanisms, clinicians have the difficult task of educating patients about unresolved concepts in the context of scenarios that are sometimes urgent or dire. In the current setting of enforcement discretion by the FDA, the agency specifies that consent “should include, at a minimum, a statement that the use of FMT products to treat CDI is investigational and a discussion of its potential risks” [75]. When weighed against the possibility of rapid relief of CDI, a patient may discount both the likelihood and magnitude of theoretical risks. Yet this potential tradeoff should serve to caution against overzealousness in the use of FMT [80]. There is never an ethical obligation to perform an experimental intervention; however, it may be ethically permissible to do so, depending on possible risks, possible benefits, and other treatment options. The decision about whether to try an unapproved treatment that offers both a chance of relatively immediate benefit and a chance of unknown long-term consequences cannot be made properly without both the clinician and the patient (1) articulating their goals for the proposed FMT treatment and (2) ensuring concordance of understanding about what is sought and, based on current knowledge, what is likely and possible. This, of course, is more complicated in a pediatric setting, where the legal decision maker—a parent or guardian—is deciding whether to accept unknown delayed risks for someone else.

5.2. Balancing patient autonomy and risk of harm

If clinicians restrict FMT procedures only to those patients who demonstrate a comprehensive understanding of the theoretical risks or who, for reasons of age or severity of disease, may reasonably choose to accept the risks of long-term effects from the transplant, some patients denied the procedure may nevertheless choose to perform it themselves. Likewise, if a policy of barring pediatric patients from receiving FMT were imposed, caregivers may seek to conduct a “home-brew” version of FMT on the patient. It is always a strong possibility that DIY donor stool would be insufficiently screened. Given this reality, a clinician may arguably consider it a form of harm reduction to perform FMT on a patient who falls outside current treatment guidelines in lieu of the DIY version that would otherwise be pursued. We are not persuaded by this stance and hold that uses outside those covered by the FDA’s enforcement discretion policy should occur predominantly in trials, with one exception discussed in section 4.4. However, this raises the issue of whether clinicians should inquire about patients’ inclination for DIY FMT when this information is not volunteered.

5.3. Balancing patient autonomy and the common good

Another question arises when a patient expresses preference for FMT for CDI, but its application is, while likely effective, outside the scope of current guidelines. For instance, if a patient has been treated for CDI with antibiotics yet develops the infection a second time, the patient may ask to skip further antibiotic therapy in favor of FMT. While a clinician’s clinical preference would be to use antibiotics in this situation, she knows that the patient is statistically more likely to develop CDI again, that FMT would likely treat the patient’s infection, and that performing the transplant would align with her patient’s stated preference. In such a context, it is understandable that she may be tempted, and/or ultimately decide, to perform the FMT. However, it must be recognized that such a decision is not currently evidence-based and does not assist in answering the question of whether FMT should become a first-line treatment in recurrent CDI. While a patient is most likely seeking individual medical benefit, a clinician has the opportunity to try to advance both the patient’s welfare and the welfare of all current and future patients by limiting the conduct of innovative practice to within clinical trials that can help generate evidence on which to base treatment guidelines [81].

5.4. Equity of access

Though instructions for and information about performing DIY FMT has proven to be abundantly available on the internet, most patients would likely prefer to have this procedure performed by a medical professional. There are, however, tangible concerns about limited or unequal access due to financial barriers to treatment. With the growing promise of FMT as a potential treatment for conditions beyond CDI, pharmaceutical companies have demonstrated interest in reaping the potential financial benefits of bacteriotherapy. A key supplier of donor stool for FMT in the United States is the non-profit stool bank OpenBiome. From 2013 to 2018, OpenBiome provided material for over 42,643 FMT procedures at nearly 1192 clinical sites throughout the US, with 12,327 stool preparations shipped and 207 new clinical site partnerships established in 2018 alone [82]. When a virtual

monopoly corners a market, potential arises for practices such as artificially-imposed shortages and/or price hikes, as well as increased vulnerability to errors in the supply chain. Furthermore, there is limited capability for additional FMT suppliers to become established, given that few facilities are currently capable of performing their own MDRO screening, as required by the 2019 FDA mandate for expanded scope of screening. Ominous signs have already begun to emerge: The price of a donor stool preparation from the company has skyrocketed from their original price of \$250 up to \$1695-\$2050 USD per treatment [83]. Physicians and patients alike have expressed growing concern about growing costs of treatment as a consequence of “hyper-regulation” [84].

Yet patients might also experience a financial burden in the context of “under-regulation.” If FMT is neither FDA-approved nor obtained in a clinical trial, most insurance companies are unlikely to reimburse for it, in keeping with longstanding policies of not paying for experimental treatments [85]. Indeed, our survey of GoFundMe for US-base appeals concerning FMT demonstrates that some patients are already having to find ways to fund their procedures and its many associated costs [70]. For example, one appeal budgeted \$5400 for a FMT, while another stated that “the hospital is demanding \$1800 before going through with the fecal transplant.” Given the small number of appeals, it is impossible to discern the source of these variations in price. Individuals who cannot afford such expenses will have an additional, financial, incentive to consider pursuing a DIY FMT, with its attendant risks.

6. Moving forward

In keeping with the available data and FDA guidance, it is prudent at this time in the US to avoid FMT as a first-line treatment for CDI. Likewise, it would be appropriate to restrict the routine (i.e., non-trial) use of FMT to CDI indications. For seriously ill patients with conditions other than CDI, who have no other available treatments and no clinical trial options, and for whom a physician believes there is sufficient evidence to believe that FMT would be more likely to cause benefit than harm, the procedure should be conducted within the framework of the FDA’s Expanded Access pathway, which allows for single patient INDs [81]. Use of Expanded Access should be exceptional and reserved for seriously ill patients with no other approved or trial options. If there is a reasonable hypothesis that FMT will provide more benefit than harm for a particular condition, then a clinical trial should be established to test that hypothesis.

It may be that a patient values the possibility of benefit from FMT more than they are concerned about the possibility of latent harm. Patients are permitted to make such decisions with regard to unproven interventions in the context of research, but only with the oversight of the FDA and an IRB, entities which also monitor reporting of adverse events. FDA and IRB oversight occurs in Expanded Access; it does not occur in innovative practice. As such, clinicians should not use FMT without an IND, except for the conditions covered by the FDA’s enforcement discretion policy. Doing so is unethical, contrary to FDA regulation, and places a clinician’s license at risk.

There is currently a need to develop uniform screening and testing requirements for donors and patients, to standardize treatment algorithms for FMT, and in particular to maintain records of its use in order to monitor short-term and long-term serious adverse reactions such as death or donor-derived infection. Understanding FMT as a subset of tissue donation might help clinicians to understand the vital necessity of these steps. While time-to-response for FMT is generally observed to be within a few days for CDI indications [3,20], there is currently a lack of a standardized, routine follow-up with FMT patients that could allow for the establishment of correlative data between FMT and late-onset adverse effects. The growing preponderance of evidence demonstrating efficacy of FMT at treating CDI may—or may not—be countered by the results of long-term follow-up, but only if such follow-up is systematically conducted. We encourage the delivery of FMTs at medical centers with specific expertise in this developing therapy. Such centers are more likely to employ clinicians and investigators who stay current with the rapidly evolving data and regulatory requirements of this treatment and who may be more vested in participating in FMT research and assessing longitudinally for long-term safety outcomes of this procedure. With more and better evidence, clinicians will be better able to decide whether to conduct FMT for specific indications.

Finally, there is a need for clinicians to strive to educate and to persuade patients not to pursue FMT as a do-it-yourself procedure any more than they would perform an organ transplant or blood transfusion at home. The relative ease of the procedure does not cancel out its risks of harm. As such, upon encountering a patient who mentions considering a “DIY FMT,” clinicians have an obligation to explain the real risks and to counsel against such a course of action. Less clear is whether clinicians should be the ones to initiate this conversation, seeking to learn if a patient is inclined to engage in such a practice, in order to counsel against it. Clinicians should not bow to patient wishes to perform unwarranted FMTs, even if the patient states that in the absence of a clinician-conducted procedure they will try a DIY approach.

7. Conclusion

At the frontier of medicine and innovation, it is difficult to balance theoretical long-term harms against immediate benefits. In the case of FMT, the situation is complicated by the reality that patients can attempt the procedure themselves with no clinical guidance or oversight. Ongoing trials and data accumulation will one day provide a clearer guide, but in the meantime, we should proceed with caution. Clinicians ought to conduct FMT only after a thorough informed consent process and only in line with the existing evidentiary base. If patients wish to pursue FMT for non-CDI indications that are not responding to standard therapies, it should be in the context of a clinical trial where individual outcomes will help to inform practice for the larger population. In exceptional cases, where the patient is severely ill and without alternative treatments (including clinical trials) and where the clinician judges that the procedure offers more possibility of benefit than of risk, FMT might be conducted under FDA and IRB oversight via FDA’s Expanded Access pathway.

We urge providers to monitor patients undergoing FMT carefully and longitudinally, and to contribute to efforts to collect long-term safety data to better understand the use of this

powerful therapy for future patients. It is human nature to attribute successes to interventions while attributing failures to the underlying disease; as such, it is not surprising that FMT is viewed as a promising treatment for myriad conditions on the basis of anecdotes. We have an ethical obligation to our current patients and to future generations of patients to conduct the research needed to arrive at evidence-based treatment decisions.

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